RBMO

COUNTERCURRENT

Will the introduction of automated ART laboratory systems render the majority of embryologists redundant?

Lorena Bori[1,2], Marcos Meseguer[1,2,3,*]

ABSTRACT

IVF techniques have changed over time with the aim of improving clinical results. Today, embryology is facing a change common to most areas of medicine, the introduction of automation. The use of automated systems in the IVF laboratory is already happening, for example, with electronic witnessing and the ranking of embryos according to their implantation potential. It is expected that in the near future, various systems in the IVF laboratory will be automated. In this way, gamete manipulation would cease to be manual and embryo culture and selection would be performed by means of microfluidics and artificial intelligence. Therefore, the tasks of the embryologist will inevitably be reduced. However, new functions related to data capture, management and analysis will emerge, along with other research skills and increased communication with other professionals and patients.

Since the first pregnancy was achieved by IVF, there have been many changes in assisted reproduction treatments. Over the past 40 years, laboratory methodologies have been rapidly updated, including intracytoplasmic sperm injection (ICSI), embryo culture extension, embryo biopsy, vitrification, time-lapse systems and electronic witnessing platforms. Further technical innovations, such as microfluidics and noninvasive embryo screening tests, are now being studied for future introduction in assisted reproduction units. Currently, we are seeing the incorporation of automation in some routine processes to minimize the number of steps and the manipulation of gametes and embryos by embryologists. Science and research invite us to constantly update our work in order to improve clinical outcomes, and the time to adapt is now.

MANUAL GAMETE MANIPULATION IS COMING TO AN END

Automation will enter the andrology laboratory in conjunction with microfluidic technologies to facilitate sperm analysis, sperm preparation and sperm selection with minimal manual input. Some preliminary studies have suggested the use of microfluidics for sperm isolation and microrobotic immobilization for ICSI (*Leung et al., 2011*; *Lu et al., 2011*). Thus, future sperm assessment may differ from current evaluation. In addition to concentration and motility, it would analyze the risk of fertilization failure and identify risks to offspring by methylation and mutation loads (*Jenkins et al., 2017*).

Robotics, computerized systems and artificial intelligence integrated with image analysis and biochemical evaluation of oocyte quality could guide patient treatment decisions and automate processes such as oocyte insemination by IVF and ICSI. Finally, systems for intelligent assessment of fertilization could be developed by means of image capture and three-dimensional reconstruction.

IN-VITRO EMBRYO CULTURE AND SELECTION IS DESTINATED TO CHANGE

Currently, in-vitro embryo culture is based on static conditions, while embryos *in vivo* are exposed to dynamic environments that provide stage-specific nutrients. New techniques of manipulation may be used to create microenvironments in the IVF laboratory. In this case, automatic microfluidic-based devices would regulate the culture medium flux, reducing the

[1] IVIRMA Valencia, Spain
[2] IVI Foundation, Valencia, Spain
[3] Health Research Institute la Fe, Valencia, Spain

*Corresponding author. E-mail address: marcos.meseguer@ivirma.com (M. Meseguer). https://doi.org/10.1016/j.rbmo.2021.10.002 1472-6483/

KEYWORDS
Artificial Intelligence
Automation
Embryologist

workload of embryologists. Ideally, the dispute between single or sequential media would end with the addition of biosensors to these devices. In this way, catabolites and supplements would be adapted to the needs of each embryo automatically.

The introduction of continuous monitoring of embryo development in IVF laboratories has already reduced, in part, the time spent by embryologists in moving embryo culture dishes and assessing embryos under optical microscopes at specific time ranges. In addition, time-lapse incubators allow for undisturbed culture conditions and the creation of evaluation and selection models based on the dynamic development of the embryo, with morphological and morphokinetic variables (Del *Gallego et al., 2019*). However, although time-lapse systems are very useful for the accurate evaluation of embryos, most of the existing embryo selection models have not achieved satisfactory results among different laboratories. This may be due to limited interobserver agreement, since the variables used, such as cell division timings or blastocyst morphology, are manually annotated.

Nowadays, embryologists could benefit from artificial intelligence (AI) and computer vision to improve their ability to select the most competent embryo for transfer. Time-lapse videos of embryo development are composed of images taken at defined time intervals (e.g. 10 or 15 minutes). These images can be processed and analyzed on a pixel-by-pixel basis. The difference between one image and the previous or subsequent image defines patterns of development. If a certain behaviour occurs frequently in the embryos that implant successfully, and not in the rest, we could identify a new marker of implantation. Computer vision-based models will apply artificial systems on images to extract information and decide which events are relevant to solve a specific question automatically. Indeed, implementing automation with time-lapse technology is already happening in the IVF laboratory for ranking embryos according to implantation potential. In parallel, automatic models on static embryo images should be developed for laboratories that have not invested in time-lapse systems.

Consideration of the visual dynamics of an embryo could be complemented by non-invasive analysis of embryo-derived factors secreted into the culture medium to assess the embryo's metabolic state. On the one hand, the metabolites involved in oxidative processes have been suggested as predictive of implantation success, in conjunction with morphokinetics (*Alegre et al., 2019*). On the other hand, several patterns of protein expression in spent embryo culture medium have been associated with stages of embryo development, morphology, and even implantation potential. Furthermore, a combination of blastocyst image analysis with proteomic information from the spent culture medium on day 5/6 of development has already been proposed as an initial model that predicts the potential for achieving a live birth (*Bori et al., 2020*).

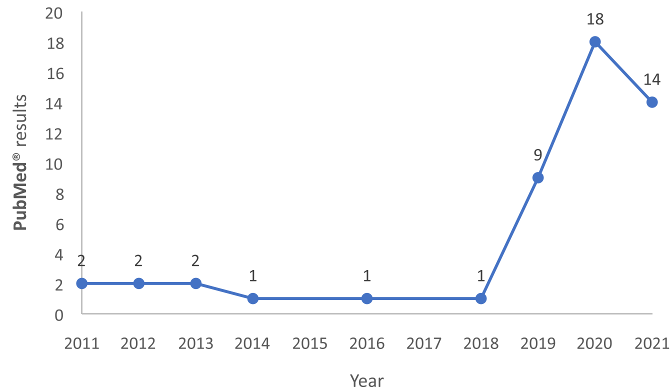

FIGURE 1 Number of publications including the terms 'Artificial intelligence' and 'IVF' in the last decade from a PubMed® search query.

In addition, the ability to identify euploid embryos by non-invasive methods, without need for trophectoderm biopsies, is improving rapidly. Novel techniques range from cell-free DNA collection for chromosomal analysis in spent culture medium to the application of computer vision to detect differences in embryo development that may reveal the embryonic health. Finally, automation will also be used for vitrification as the last step of microfluidic-based devices.

A complex artificial intelligence system based on a combination of microfluidics, biomarkers of embryo metabolism, image analysis and non-invasive PGT-A will serve to create an embryo ranking for each embryo cohort and reduce time to pregnancy.

THE EMBRYOLOGIST'S ROLE WILL ADAPT IN THE FACE OF AUTOMATION

Automation is entering embryology, as revealed by the increase in publications based on artificial intelligence in IVF laboratories (FIGURE 1). In the near future, data collection could be performed automatically in laboratories by voice recognition in electronic medical record systems. In the same way, a facial recognition system could be installed at the workstations that would automatically record the date, time, process and operator. Even the preparation of culture dishes and sampling of the medium for quality control could be automated. In this way, key performance indicators will become increasingly complex and numerous. Big data-based systems could be used as an early warning to detect changes in equipment or operator performance. In addition, AI-driven technologies could improve quality systems in all laboratories, regardless of the number of cycles, by providing sufficient information to optimize procedures. Thus, data integration will encompass all clinical and technical variables to enable AI-based algorithms to 'learn' from these data sets and adjust performance on an ongoing basis.

Electronic witnessing systems are a form of automation used daily in IVF laboratories. Their incorporation reduced the time spent by embryologists and improved the traceability of samples (*Rienzi et al., 2015*). In the short term, it is expected that similar automated systems will be introduced for quality assurance and machine supervision. This will also reduce the time spent by laboratory operators on equipment maintenance and simplify routine procedures.

Automation will increase in several clinical processes, such as embryo scoring, oocyte denudation, and even fertilization checks. Embryo morphology and morphokinetics will undoubtedly be delegated to AI and computer vision applications, which will be able to detect small developmental aberrations that may affect reproductive success. In addition, information from '-omics' sciences, such as genomics, epigenomics or proteomics will add further value to these novel applications. However, more complex procedures, such as ICSI, trophectoderm biopsy, and vitrification, may not be fully automated in the near future due to their highly technical and variable nature. Although there are researchers working on these types of tools, as they are the most difficult and time-consuming tasks. In any case, the use of an automatic technique should be tested prior to its clinical application to ensure its safety.

These novel technologies will provide us with a wealth of information that we can use for further research and advancement. Nonetheless, the key question is: are embryologists ready for tomorrow? It is inevitable that the implementation of automated and rapid systems will reduce the future demand for embryologists. However, when key tasks are automated, other novel tasks will be created around the increasing amount of data that will be generated per embryo. Therefore, the expertise of embryologists will always be necessary to ensure the successful implementation of any new technology.

The embryologist's profession will inevitably change. There may come a time when human manipulation of embryos will no longer be necessary and all processes will be robotized. In this way, embryology would be much more technological, focused on advising computer scientists and engineers on the development of devices for embryo manipulation. The new role of embryologists will involve exploring the data and determining its relevance, deciding how to use the huge amount of data collected and in what way to combine it to provide an accurate diagnostic of the competence of an embryo.

Embryologists will need to understand how large data sets from different sources, such as a combination of stimulation protocols, patient characteristics, embryo developmental events, and even environmental conditions, are processed using new technologies. Additionally, they will learn how to interpret results, with the capacity to recognize biological and clinical information generated by data fusion. The knowledge gained will facilitate communication between embryologists and patients. The embryologist must be able to broadcast what is 'in action' in the laboratory, to make this information accessible to a growing demand from patients who increasingly want to understand all the procedures occurring in this 'black box' between oocyte retrieval and embryo transfer. The new tasks that embryologists will face will require additional knowledge in statistics and database management.

Future embryologists, apart from having a basic knowledge of the complexity of in-vitro fertilization, should have good communication skills as their new role will also focus on advising colleagues and patients on recommended treatment options. Nonetheless, a few embryologists may still play a more active role in practical laboratory work in the daily clinical routine.

In conclusion, although automated ART laboratory systems will reduce the time spent by embryologists on their current tasks, they will perform new functions focused on clinical and biological aspects of patient care, including quality control and assurance.

REFERENCES

Alegre, L., Gallego, R. Del, Arrones, S., Hernández, P., Muñoz, M., Meseguer, M. **Novel noninvasive embryo selection algorithm combining time-lapse morphokinetics and oxidative status of the spent embryo culture medium.** Fertil. Steril. 2019; 111: 918–927

Bori, L., Dominguez, F., Fernandez, E.I., Gallego, R Del, Alegre, L., Hickman, C., Quiñonero, A., Nogueira, M.F.G., Rocha, J.C., Meseguer, M. **An artificial intelligence model based on the proteomic profile of euploid embryos and time-lapse images: a preliminary study.** RBMO 2020; 42: 340–350

Gallego, R. Del, Remohí, J., Meseguer, M., Affiliations, A., Valencia, I.G. **Time-Lapse Imaging : The State of the Art.** Biol. Reprod. 2019; 101: 1146–1154

Jenkins, T.G., Aston, K.I., James, E.R., Carrell, D.T. **Sperm epigenetics in the study of male fertility, offspring health, and potential clinical applications.** Syst. Biol. Reprod. Med. 2017; 63: 69–76

Leung, C., Lu, Z., Esfandiari, N., Casper, R.F., Sun, Y. **Automated sperm immobilization for intracytoplasmic sperm injection.** IEEE Trans. Biomed. Eng. 2011; 58: 935–942

Lu, Z., Zhang, X., Leung, C., Esfandiari, N., Casper, R.F., Sun, Y. **Robotic ICSI (Intracytoplasmic Sperm Injection).** IEEE Trans. Biomed. Eng. 2011; 58: 2102–2108

Rienzi, L., Bariani, F., Dalla Zorza, M., Romano, S., Scarica, C., Maggiulli, R., Nanni Costa, A., Ubaldi, F.M. **Failure mode and effects analysis of witnessing protocols for ensuring traceability during IVF.** Reprod. Biomed. Online 2015; 31: 516–522

Received 15 September 2021; received in revised form 28 September 2021; accepted 4 October 2021.